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ORIGINAL PAPER

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Molecular modeling of noncompetitive antagonists of the NMDA receptor: proposal of a pharmacophore and a description of the interaction mode

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Abstract Since the three-dimensional structure of the NMDA receptor has not been determined experimentally, indirect computer-assisted molecular modeling techniques appear to be of great usefulness in the characterization of the common pharmacophore of all NMDA receptor noncompetitive antagonists, despite their structural differences. Indeed, the conformational analysis of three different chemical families (MK801, PCP, dexoxadrol and their analogues), has allowed us to visualize the different conformations and configurations of each molecule. Superimposition with configurations 1 and 2 of the MK801 molecule has allowed us to propose active conformations and thereafter a geometrical characterization of the pharmacophore, especially the determination of the orientation of the nitrogen lone pair (NLP) related to the phenyl. On the other hand, electrostatic studies, combined with geometrical features, have allowed us to schematize the interaction mode of an active conformation to the binding site. Finally, studies of the molecular lipophilic potential (MLP) have provided us information on the position of lipophilic and hydrophilic zones of the pharmacophore.

Keywords Noncompetitive antagonists · NMDA receptor · Pharmacophore · Conformational analysis · MEP · MLP

Introduction

Several studies made on the NMDA receptor have shown that it is involved in the pathology of neurological and neurodegenerative disorders such as epilepsy, Huntington's and Alzheimer's diseases, schizophrenia, etc [1, 2]. The NMDA receptor possesses a variety of potential drug-binding sites. In addition to the L-glutamate recognition site, which is the target for a number of synthetic competitive antagonist drugs, MK801 and the dissociative anesthetics, PCP, ketamine and dexoxadrol, act as noncompetitive antagonists at a site associated with the cation channel. Thus, it has been suggested that these antagonists could have an important therapeutic potential for neurological diseases [3, 4, 5, 6, 7, 8, 9]. Based on the hypothesis that there exists a common structure, active in the central nervous system, consisting of an aromatic group and nitrogen atom, several geometric models have been proposed. In these models, the receptor sites were localized and several authors have tried to describe geometrically the interaction mode [10, 11, 12]. The major problem confronted in trying to determine the pharmacophore characteristics has been the conformational flexibility of the majority of the ligands used. The general method adopted in most cases is the superimposition of flexible molecules to the most rigid molecule, which is chosen as a reference [10, 11, 12, 13, 14, 15, 16, 17, 18]. Among the attempts to design rigid molecules, the synthesis of the aminohexahydrofluorene (AHF), a rigid analogue of PCP, allowed the determination of the phenyl orientation (phenyl in axial position). [19] However, the orientation of the nitrogen lone pair (NLP) in relation to that of phenyl ring remained unknown.

Even if dibenzocycloalkenimines (MK801 and its analogues), the arylcyclohexylamines (PCP, ketamine and their analogues), and the dioxolanes (dexoxadrol and its analogues) represent three different chemical families, all pharmacological results indicated that MK801, PCP and the dexoxadrol act at the same receptor [20, 21, 22, 23, 24, 25, 26]. Only, in these pharmacological studies, compounds' activities are, most of the time, presented with a specification of absolute configurations (R and S) of asymmetric carbons of the enantiomers, while ignoring the configuration of the nitrogen atom. However, the knowledge of this latter configuration is essential for the

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localization of the nitrogen atom binding site at the receptor. This is, therefore, the principal target in this work.

To accomplish this task, we have decided to implement methods of indirect molecular modeling so as to define a common pharmacophore to MK801, PCP and to the dexoxadrol as well as to their analogues. At first, we have built molecules on the basis of published qualitative structure–activity relationships. We have, then, realized a conformational analysis with a focused interest on the different orientations of the NLP, in its relation to the phenyl ring, which seems to be important for the activity. We have chosen MK801 as a reference molecule because it is the most active and rigid molecule. Finally, the superimposition of active and inactive molecules to MK801 in its two forms, called in this paper configuration 1 and 2, led to the proposal of a geometrical pharmacophore.

Secondly, we have studied the molecular electronic and lipophilic characteristics. We have realized 3D and 2D molecular electrostatic potential maps (MEP) and 2D molecular lipophilic potential maps (MLP) (in parallel planes to the phenyl ring intervening in the superimposition). We have, thus, attempted to define electronic and lipophilic characteristics of the pharmacophore.

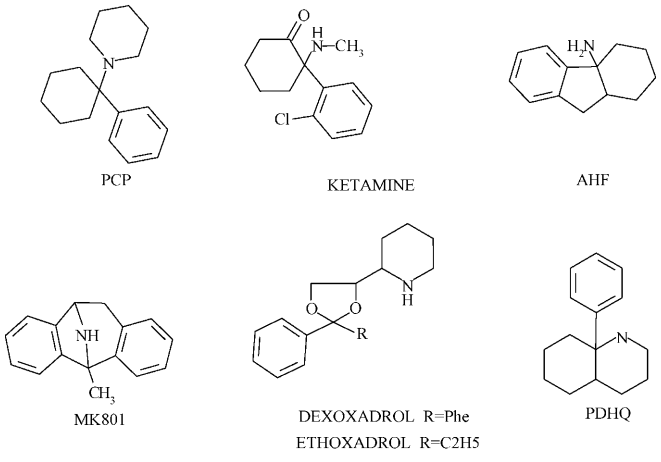


Fig. 1 Series of active molecule

Methods and materials

The software that has been used for this work is : MacroModel, [27] CHEM-X [28] and ML. [29].

MacroModel was used to build molecules and to optimize their geometry through a minimization of molecular mechanic energy until a local minimum was attained. The force field used in MacroModel was MM2 (87) developed by Allinger [30] and modified by Still [31]. The conformational analysis used the program option MULTIC (multiconformer) and MM2. The variation step of torsion angles was 30° in an area of 360°. The conformers were minimized until a RMS gradient (root mean square) <0.024 kcal Å by using diagonal blocks of the Newton–Raphson method (BDNR), terminal atoms are able to move freely (TAMOV on). The conformers were then completely minimized until an RMS gradient <0.0024 kcal Å by using the Newton–Raphson method and the complete matrix (FMNR). All the unique conformers situated in an energy range of 5.981 kcal above the global minimum were listed and classified by increasing energy.

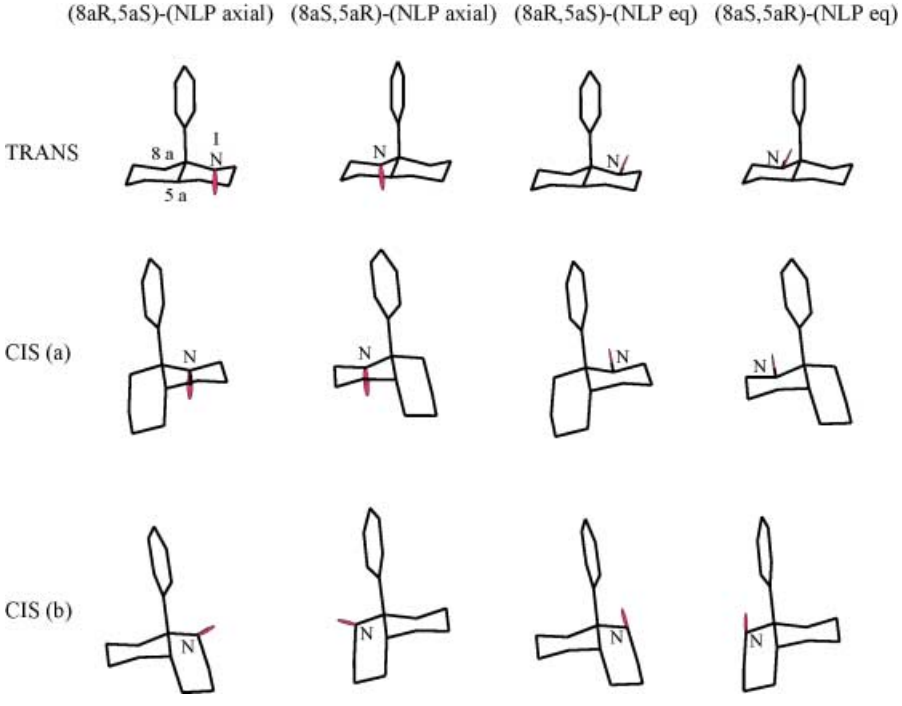
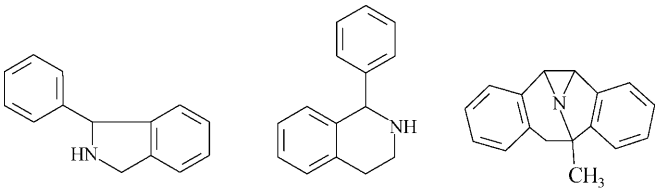


Fig. 2 12 configurations of PDHQ. NLP eq: the NLP is in the equatorial position. NLP axial: the NLP is in the axial position



a b c

Fig. 3 Inactive molecules a, b, and c

Table 1 Activities of *cis*- and *trans*-PDHQ enantiomers [39]

Molecule	IC50 (nM)
(+) 8aR *cis*-PDHQ	158.7±24
(–) 8aS *cis*-PDHQ	467.4±52
(+) 8aS *trans*-PDHQ	94.6±28
(–) 8aR *trans*-PDHQ	66.3±9.7
PCP	35
MK801	1.4

The files obtained (MacroModel format) were then converted into CSSR format files and exported to CHEM-X.

CHEM-X was used for rigid and flexible superimposition methods. The CHEM-QM module was used for the calculation of atomic charges with semiempirical quantum mechanical methods. It is an interface with especially the MOPAC [32] and AMPAC [33] programs in conjunction with MNDO as Hamiltonian. Two- and three-dimensional electrostatic potential maps were generated with the program VSS, [34] also available in CHEM-QM.

Molecular lipophilic potential maps were generated using the MLP program written in Turbo Pascal by Croizet [35] on an original concept introduced by Audry et al. [36] Lipophilic fragment constants were taken from the work of Broto et al. [37] and attributed automatically to atoms constituting molecules [38].

Two series of molecules, on which we have precise pharmacological data, were studied. The first series, constituted of seven molecules having a high affinity to the NMDA receptor, is shown in Fig. 1. And since we have at our disposal activities (IC50) of four configurations 8aR and 8aS of the *cis* and *trans* isomers of 8a-phenyldecahydroquinoline (8a-PDHQ) [39], we have examined the different configurations in the case of axial and equatorial NLP. 12 configurations have been determined, as shown in Fig. 2. The PDHQ activities are given in Table 1 [39]. The second series is shown in Fig. 3. It consists of three molecules denoted a, b, and c in this paper. They are devoid of activity at this same receptor, or show only very weak activity [40, 41, 42].

A dummy atom (DA) was placed 2.6 Å tetrahedrally from the nitrogen atom to represent an interaction between a protonated nitrogen atom and its binding site [10, 25, 39, 41, 43].

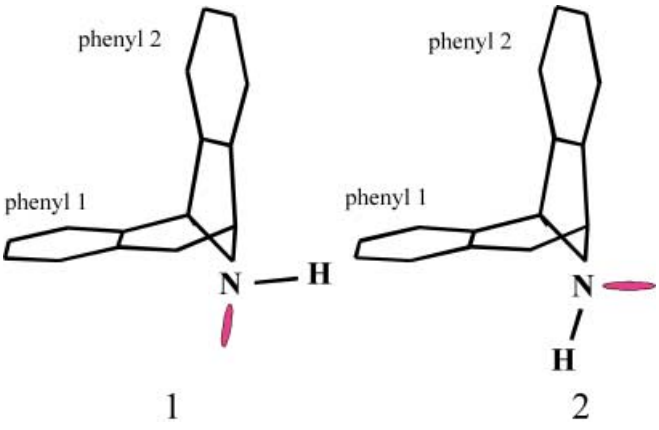


Fig. 4 Two possible configurations of MK801 (configuration 1 and 2)

Results and discussion

The conformational and stereochemical analysis generated a series of conformations and configurations for each molecule. Thus, the MK801 molecule, that was constructed in its configuration (1R,5S), is represented by two forms called hereafter configurations 1 and 2, as shown in Fig. 4. These two forms are distinguished only by the absolute configuration of the nitrogen atom, in other words, by the orientation of the NLP. The difference in energy between the two configurations is 0.337 kcal.

Being the most rigid molecule and the most active of the series, [20, 21] MK801 has been chosen as a reference model for the superimposition of the less rigid molecules, knowing that the interaction of a molecule with PCP binding sites necessitates a nitrogenous group and an aromatic group. This latter appears to be responsible for the arylcyclohexylamines' biochemical selectivity [43, 44, 45], and the stabilization of the receptor structure (protein) [46]. On the other hand, Lyle et al. had shown that the reduction of phenyl 2 (Fig. 4) is well tolerated and in some cases is beneficial. However, the reduction of phenyl 1 affords analogues with reduced binding affinity [47]. On this basis, we have chosen phenyl 1 (Fig. 4) as a phenyl of superimposition because it is certainly the one that interacts with the receptor [47]. We have, then, superimposed the phenyl, the nitrogen atom and the DA of each molecule, relative to phenyl 1, the nitrogen atom, and the DA of configurations 1 and 2 of MK801. The fact that MK801 exists in two forms suggests that the pharmacophore may correspond to one of the two MK801 configurations: 1 or 2. Thus, all the conformations and configurations with their different NLP orientations were superimposed on configuration 1 or 2 of MK801. For example, for *trans* and *cis*(a) isomers of 8a-PDHQ, the configurations with the NLP in the equatorial position, were superimposed on configuration 1 of MK801, and those with the NLP in the axial position were superimposed on configuration 2 of MK801. How-

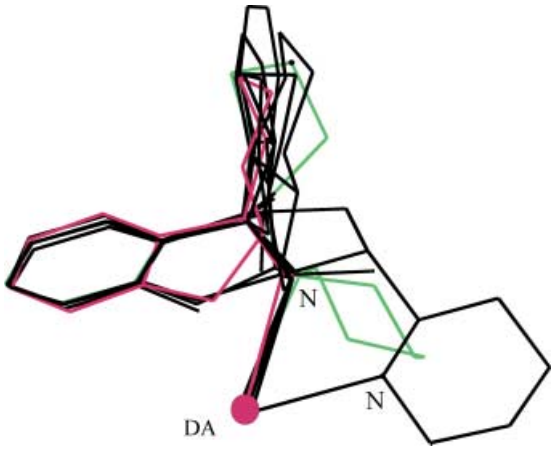


Fig. 5 PCP, ketamine, dexoxadrol, PDHQ, and AHF superimposed to configuration 1 of MK801. PCP molecule is *green*, AHF is *purple*, and the rest of the molecules are *black*

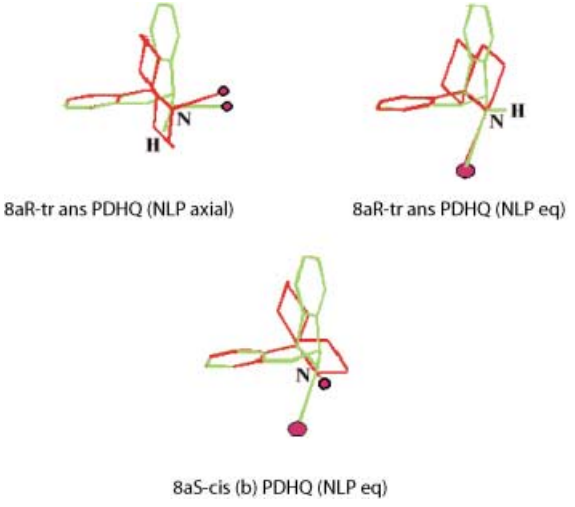


Fig. 6 MK801 is in *green* lines and PDHQ is in *red* lines. The dummy atoms (DA) are designated by filled *purple* circles. (NLP axial, or eq) designate the axial and equatorial positions of NLP. 8aR-*trans* PDHQ configurations (NLP axial) and (NLP eq) are superimposed respectively to configurations 2 and 1 of MK801, *d*(DA–DA)=1 Å and 0 Å. The 8aS-*cis*(b) PDHQ (NLP eq) is superimposed to configuration 1 of MK801, d(DA–DA)=3 Å

ever, all configurations of *cis*(b) were superimposed on configuration 1 of MK801 because their NLP orientation is closer to configuration 1 than 2.

The best superimpositions are obtained with configuration 1 of MK801. These are shown in Fig. 5.

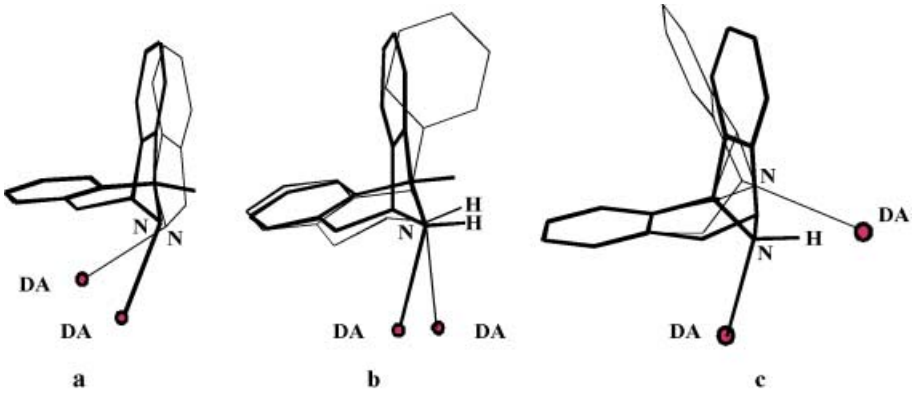
We note that the superimpositions undertaken with configuration 2 of MK801 did not give good results [48]. Indeed, among the 12 configurations of 8a-PDHQ, the most active one, 8aR-*trans* PDHQ (Table 1), gives the best superimposition with configuration 1 of MK801 in the case of the equatorial position of NLP and, at the same time, the worst superimposition with the configuration 2 of MK801 in the case of axial position of NLP. However, the least active configuration, 8aS-*cis* PDHQ, gives the worse superimposition with configuration 1 of the MK801 in the case of the *cis*(b) isomer, so, the DA are at a distance of 3 Å. These superimpositions are shown in Fig. 6.

The superimposition of molecules a, b, and c to configurations 1 and 2 of MK801 confirms that the inactivity of these three molecules, as Leeson et al. have suggested, stems mainly from the NLP orientation [41]. Using the method of superimposition, we have demonstrated that the NLP orientation, for the three compounds a, b and c, differs very clearly and precisely from that in configuration 1 of MK801. These superimpositions are shown in Fig. 7.

The fact that compound c does not give good superimposition to configuration 1 of MK801 (the dummy atoms are divergent), but on the other hand, gives a good superimposition to configuration 2 (Fig. 8), supports the hypothesis that the pharmacophore may be conformed to configuration 1 of MK801, and eliminates the possibility with configuration 2 of MK801. Especially it implies that, in compound c, all nitrogen substituents are blocked into the ring, which means that the NLP possesses only one orientation.

These inactive compounds possess all required features for activity, except that they cannot be superimposed on configuration 1 of MK801 and sometimes are well superimposed on configuration 2. On the other hand, the good superimposition of active molecules on configuration 1 of MK801 and not on configuration 2 of MK801 suggests that having geometrical characteristics

Fig. 7 Molecules a, b, and c (in fine line) superimposed to configuration 1 of MK801 (in thick line)



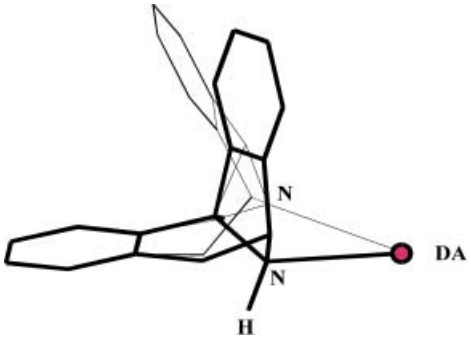


Fig. 8 Compound c (in fine lines), superimposed to configuration 2 of MK801 (in thick lines)

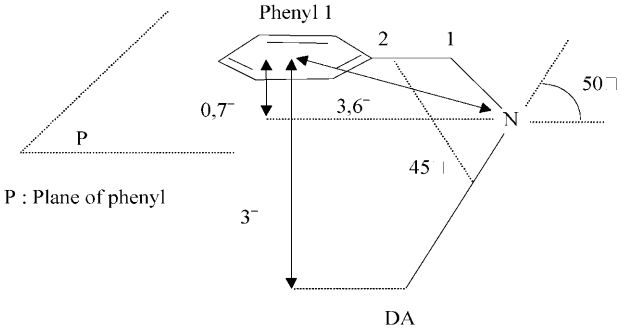


Fig. 9 Geometric characteristics of the proposed pharmacophore for the NMDA/PCP site

consistent with configuration 1 of MK801, especially the NLP orientation, is an essential factor for a compound to be active at the receptor.

Thus, we can conclude that the pharmacophore of the NMDA receptor corresponds to configuration 1 ofMK801, rejecting the possibility corresponding to configuration 2.

The pharmacophore is shown in Fig. 9. It is characterized by the following geometrical properties:

- The gap between the nitrogen atom and the plane of the phenyl is 0.7 Å.
- The gap between the DA and the plane of the phenyl is 3 Å.
- The distance between the phenyl center and the nitrogen atom is 3.6 Å.
- The angle formed by the molecular determinant and by the plane of the phenyl is 50°.
- The dihedral angle DA–N–C(1)–C(2) is 45°.

Several previous studies had proposed the NMDA pharmacophore structure. [49] However, the discussion of the different and possible NLP orientations existing in the same molecule remains incomplete. For example, it has always been considered that MK801 has only one form for one enantiomer. However, as we have noted above, MK801 in one enantiomer (1R,5S) possesses two NLP orientations illustrated by two configurations 1 and 2. So, a comparison of the pharmacophore generated with

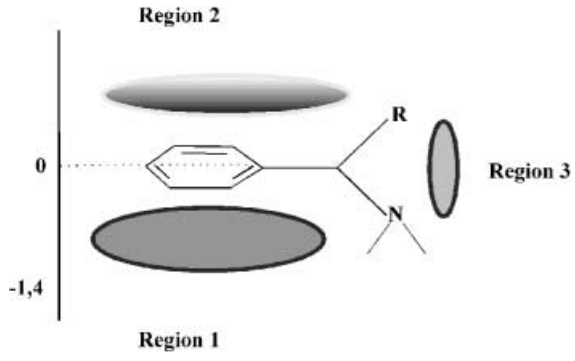


Fig. 10 The three regions of geometric pharmacophore (R: an aromatic ring for MK801 and dexoxadrol, and saturated cycles for the remained molecules)

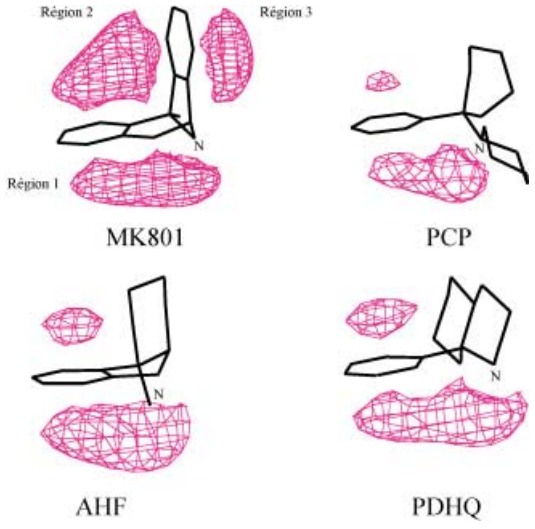


Fig. 11 3D maps of MEP

previous investigations seems to show the same features [25, 50, 51]. However, a difference is revealed in the orientation of the NLP, which has led to a different nitrogen binding site at the receptor.

In order to determine the physico-chemical characteristics of the pharmacophore we have explored two molecular properties:

- Electronic properties by the calculation of the MEP
- Hydrophilic and lipophilic properties by the calculation of the MLP

MEP

The MEP was calculated for the active molecules, in their conformations retained by the superimposition with MK801. According to the three-dimensional maps, we observe three negative zones of electrostatic potential designated in Fig. 10 by regions 1, 2, and 3. The extrema of the most important zones of negative electrostatic potential, for all molecules, are situated in region 1–1.4 Å

from the plane of phenyl 1 (Fig. 10). Furthermore, it is in region 1 that we have observed a perfect analogy in values and in positions of the extrema.

In fact, for molecules that do not contain any oxygen atoms, MK801, PCP, AHF and PDHQ, shown in Fig. 11, we observe an important negative zone, common to the four molecules, due to the electrons of the NLP and of the phenyl 1 ring. The extrema of this zone are situated –1.4 Å from the plane of phenyl 1.

For molecules containing atoms of oxygen, the ketamine and the dexoxadrol, shown in Fig. 12, the most important negative zone is centered in the level of the oxygen atoms. The extrema of this zone are also situated –1.4 Å from the plane of phenyl 1.

Values of extrema corresponding to nitrogen atom are included between –25 and –31 kcal mol^{-1}, those corresponding to electrons of phenyl 1 are included between –16 and –18 kcal mol^{-1} (except for the ketamine where it is –10 kcal mol^{-1}) and those corresponding to oxygen atoms are included between –40 and –43 kcal mol^{-1}. Thus, region 1 is considered as the most important zone in the pharmacophore.

In order to find the limit of the negative electrostatic zone in region 1, we have traced 2D maps at different levels (H) from the phenyl 1 plane, in the case of configuration 1 of MK801 (H : –3 Å, –3,5 Å, –4 Å, –5 Å, –6 Å and –7 Å). We have stopped at –7 Å because from there, the electrostatic potential becomes null. Finally, we have gathered the different levels in the same map, as shown in Fig. 13.

We have, therefore, attempted to schematize the interaction mode between an active conformation and the receptor, while taking into account its electronic and geometrical characteristics. The schematization is shown in Fig. 14.

The maximum and the minimum of the MEP are situated respectively at –1.4 Å and –7 Å. This translated the maximum and the minimum of the interaction potential between the ligand and the binding site. Thus, with respect to the van der Waals interactions, an aromatic–aromatic interaction, π–π type, is limited in the zone between –3 Å and –4.5 Å from the plane of phenyl 1, and

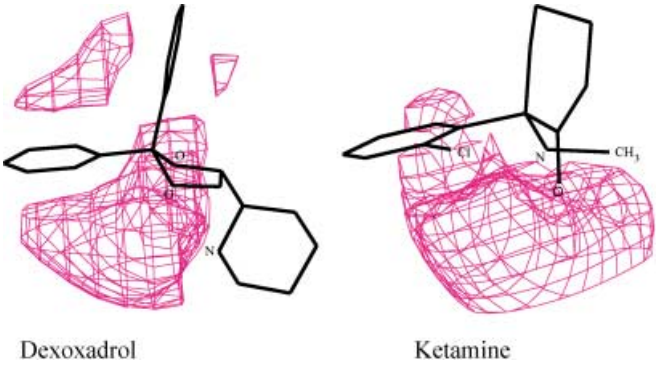


Fig. 12 3D maps of MEP

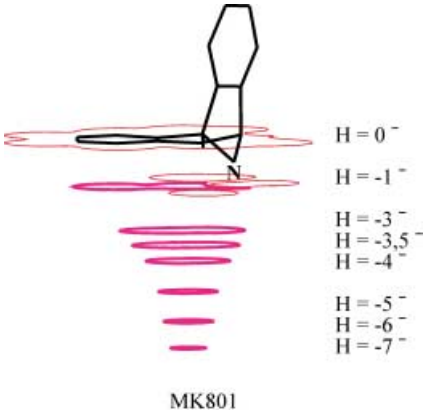


Fig. 13 2D electrostatic potential maps (negative zones are in *purple* lines, positive zones are in *red* lines)

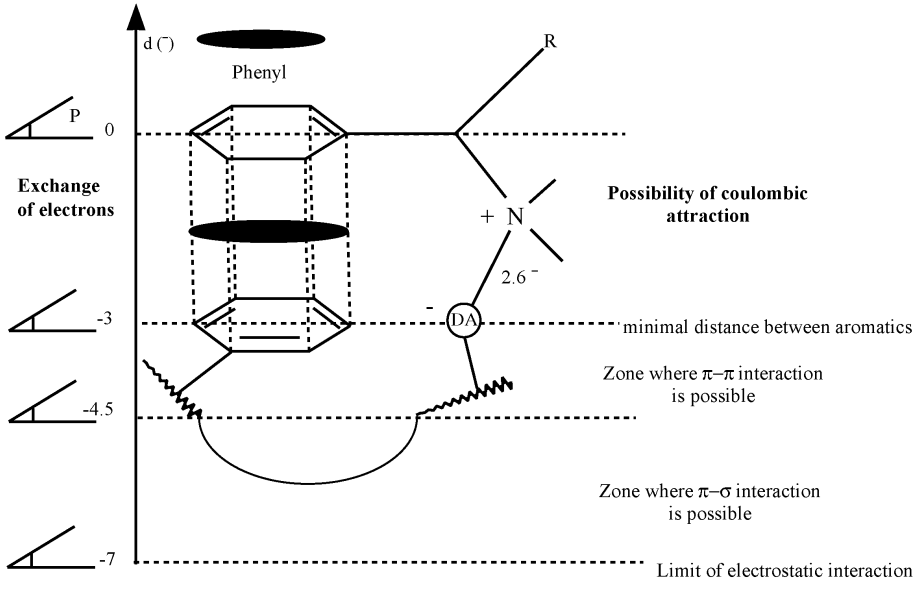


Fig. 14 Electrostatic characteristics of the proposed pharmacophore and hypothetical interactions with the receptor

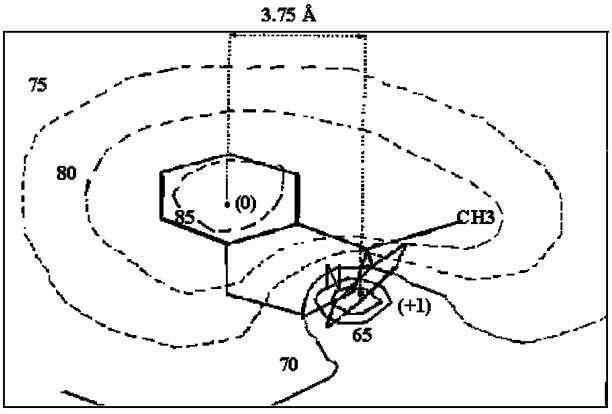


Fig. 15 2D molecular isolipophilic potential maps, calculated for configuration 1 of MK801. The lipophile zones are in discontinuous lines and the hydrophile zones are in continuous lines. The levels (*Z*) are giving into brackets

another, type σ–π, between –4.5 Å and –7 Å. [48] These results agree with those of Burley et al. [46]

MLP

The molecules have been projected onto the plane of phenyl 1.

Using a computer program developed by Croizet [35, 38], we have calculated and traced 2D isolipophilic maps in planes *Z*, parallel to the plane of phenyl 1. This program has also allowed us to calculate the extrema of the lipophilic zones PL(L) and the hydrophilic zones PL(H) as well as the distance separating them. The 2D isolipophilic maps calculated for configuration 1 of MK801, are shown in Fig. 15.

The extrema of hydrophilic zones are situated in the plane *Z*=1 Å for most of the molecules, except AHF and dexoxadrol where they are situated in planes *Z*=2 Å and *Z*=3 Å. The extrema of the lipophilic zones are situated in the plane *Z*=0 Å in the case of MK801, the dexoxadrol and PDHQ, in the plane *Z*=2 Å in the case of the ketamine and AHF and in the plane *Z*=1 Å in the case of PCP. It is therefore impossible to conclude anything from these observations. However, distances that separate the lipophilic zones and the hydrophilic zones are situated between 3 Å and 3.75 Å, which is relatively homogeneous.

Conclusion

Despite the difference in structure between MK801, PCP, dexoxadrol and their analogues, we were able, using molecular modeling techniques, to define geometrical, electronic, and lipophilic characteristics of the common pharmacophore of these three chemical families, which act at the same receptor site. The superimposition of active and inactive molecules on configurations 1 and 2 of MK801 demonstrated that the pharmacophore corresponds rather to configuration 1 than to configuration 2. In this pharmacophore, which comprises a phenyl, an atom of nitrogen and the DA, we have determined with precision the orientation of the NLP relative to the phenyl. So, the distance between the center of the phenyl and the nitrogen atom is 3.6 Å, and the gap between the DA and the plane of the phenyl is 3 Å. The electronic characteristics of the pharmacophore are provided by the calculation of the MEP. The maximum and the minimum of the MEP are situated respectively at –1.4 Å and –7 Å to the phenyl 1 plane. This translated the maximum and the minimum of the potential of interaction between the ligand and the binding site. Thus, for the van der Waals interactions, we have a limited zone of π–π interaction type between –3 Å and –4.5 Å from the plane of phenyl 1, and another type σ–π between –4.5 Å and –7 Å. The pharmacophore is also characterized by hydrophilic and lipophilic zones at a distance of 3 Å to 3.75 Å.

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